REMARKS

Claim 4 is pending in this application. Claim 4 has been rejected. The Title of this application has been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

I. Withdrawn Objections and Rejections

Applicants are pleased to acknowledge that the objection to the specification at page 2, has been withdrawn.

Applicants further acknowledge the withdrawal of the rejection of 35 U.S.C. § 112, first paragraph, in view of the canceled claim 2.

II. Objection to the Specification

The Examiner has objected to the disclosure, because it is suggested that the title of the invention is not descriptive. The title has been amended in accordance with the Examiner's suggestion. Support for this amendment is found throughout the specification and at page 4, lines 21-23, and page 5, line 4. No new matter has been added by this amendment.

III. Rejection of Claim 4 under 35 U.S.C. § 112, first paragraph

Claim 4 has been rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner suggests that claim 4 recites a method of inhibiting the processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brains of patients with Alzheimer's disease comprising administering to a patient an agent which decreases processing of amyloid precursor protein into amyloid β peptides wherein said agent is identified by contacting NTN2 cells with the agent and measuring levels of amyloid β peptides formed in the endoplasmic reticulum (ER) of the cells. The Examiner suggests that the specification of the instant application does not teach any methods or working examples wherein a patient is administered an agent which decreases processing of amyloid precursor protein into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in brains of patients with Alzheimer's disease.

Applicants respectfully traverse this rejection.

Section 2107.02 of the MPEP states "if reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process. Section 2107.02 of the MPEP further states "The applicant does not have to prove that a correlation exists between a particular activity and an assorted therapeutic use of a compound as a matter of statistical certainty, nor does he or she have to provide actual evidence of success in treating humans where such a utility is asserted. Instead, as the courts have repeatedly held, all that is required is a reasonable correlation between the activity and the asserted use *Nelson v. Bowler,* 626 F.2d 853, 857, 206 USPA 881, 884 (CCPA 1980).

The Examiner acknowledges that the specification teaches the use of the NT2N system to modulate APP processing. Specifically, the Examiner acknowledges that NT2N neurons are metabolically labeled with [^{35}S] methionine in the presence or absence of Brefeldin A (BFA). Further acknowledged is that the specification teaches that in the absence of BFA, full length

APP, APPβ, and Aβ are recovered from cell lysates, while APPα, APPβ and Aβ are detected in the media of NT2N neurons. Further, in the presence of BFA, full length APP, APPβ and Aβ are recovered from NT2N cell lysates but the secretion of APP, APPβ and Aβ into the medium is completely abolished in the presence of BFA. The specification further is acknowledged to teach that an ER-retention signal is placed in APP695 wherein this lysine motif signal is sufficient to retain heterologous transmembrane proteins in the ER and intermediate compartment. Further acknowledged is that ER retention of APP by the KK retention signal blocks Aβ secretion.

As well known to those of skill in the art, the NT2N cell model system is a predictable system used to study APP processing in neurons. NT2N cells have been reported to produce intracellular Aβ, as described in the specification at page 5, lines 25-32. NT2N neurons have been found to express the isoform of APP expressed almost exclusively in the CNS, and generate detectable intracellular levels of both $A\beta_{40}$ and $A\beta_{42}$, see specification at page 5, lines 25-32. Further, NT2N cells constitutively produce and secrete Aβ. The detection of APPβ in the cell lysate of NT2N neurons, together with the presence of

$A\beta_{40}$ and $A\beta_{42}$ establish that an intracellular β-secretase pathway exists in these cells, see specification at page 8, lines 20-23. The Examiner has acknowledged that the specification teaches the use of the NT2N system to study APP processing and that agents which modulate APP processing by decreasing APPβ and Aβ can be identified by determining their effect on the levels of APPβ and $A\beta_{42}$ produced by β-secretase and γ-secretases in the ER of neuronal cells. It is further taught that the amyloid precursor protein is processed into amyloid β peptides found in neuritic plaques and vascular deposits that accumulate in the brains of patients with Alzeheimer's disease, see page 4, lines 25-26 of the specification. Thus, agents which inhibit levels of APPβ and $A\beta_{42}$ may be useful in reducing neuritic plaques and vascular deposits associated with the amyloid β peptides. There is more than a reasonable correlation between the activity taught in the specification and the asserted method of claim 4. Based upon the teachings of the instant invention, one of skill in the art would routinely be able to administer an agent which decreases processing of amyloid precursor protein into amyloid β peptides, such as those found in neuritic plaques of Alzeheimer patients. Thus, the demonstrated efficacy of the claimed method of contacting NTN2 cells with an agent suspected of decreasing

amyloid precursor protein processing to inhibit the processing of amyloid precursor protein into amyloid β peptides, in the specification is clearly suggestive to one skilled in the art that the claimed method would work in a patient.

The Examiner has further cited prior art as exemplary in suggesting that there is no known cure for Alzheimer's disease. The Examiner suggests that Brinton et al. 1998 Pharmaceutical Res 15(3):386-398, indicates that cholinergic pharmaceuticals only modestly improve cognitive function, have short lived effects, and are in the early stages of development. Brinton et al. is further suggested to mention that unlike animal studies with nerve growth factor, human trials have not been successful. Additionally, Roses, 2000 Lancet 355:1358-1361 is suggested to disclose that "if an effective treatment were to be developed for a common form of the illness, it might not work for all patients, especially those with rare mutational forms of Alzheimer's disease". Roses is also suggested to recite that a patient's response to a drug may depend on other factors such as drug distribution, absorption, concentration, metabolism and elimination. Applicants disagree with the characterizations of these references, and also to their relevance in light of the 35 U.S.C. § 112, first paragraph rejection.

Brinton et al. is a review article which discusses the advances and challenges in the prevention and treatment of Alzheimer's disease.

Roses is a review article which discusses future drug development and delivery in light of efficacy, safety and adverse drug reactions in patients. Roses suggests at column 1, paragraph 3, that in general diseases are collections of symptoms and signs (phenotypes) that appear to be similar and for many diseases there is no accurate single diagnostic test. Roses also speculates that if an effective treatment were to be developed for a common form of Alzheimer's it may not work for all Alzheimer's patients.

In accordance with MPEP 2107.01, office personnel should be especially careful not to read into a claim unclaimed results, limitations or embodiments of an invention. See *Carl Zeiss Stiftung v. Renishaw PLC* 945 F2d 1173, 20 USPQ2d 1094 (Fed Cir 1991); *In re Krimmel,* 292 F2d 948, 130 USPQ 215 (CCPA 1961). Doing so can inappropriately change the relationship of an asserted utility and raise issues not relevant to examination of that claim, MPEP 2107.

Applicants respectfully point out that claim 4 is drawn to a specific method of inhibiting the processing of amyloid precursor protein into amyloid β peptides. Applicants respectfully assert that the Examiner has inappropriately read into claim 4, unclaimed results, limitations or embodiments of an invention. Applicants are not claiming a cure to Alzheimer's disease. None of the recited art addresses modulation of the processing of amyloid precursor protein into amyloid β peptides. Accordingly withdrawal of these rejections under 35 U.S.C. § 112, first paragraph, is therefore respectfully requested.

IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly,

favorable reconsideration and subsequent allowance of the pending claim is earnestly solicited.

Respectfully submitted,

Jane Massey Licata
Registration No. 32,257

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Licata & Tyrrell P.C.
66 E. Main Street
Marlton, New Jersey 08053

(856) 810-1515